(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 805 149 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
**05.11.1997 Bulletin 1997/45**

(21) Application number: **95937174.1**

(22) Date of filing: **24.11.1995**

(51) Int. Cl.[6]: **C07D 241/08**, A61K 31/495

(86) International application number:
**PCT/JP95/02391**

(87) International publication number:
**WO 96/16947 (06.06.1996 Gazette 1996/26)**

(84) Designated Contracting States:
**BE CH DE DK ES FR GB IT LI NL SE**

(30) Priority: **01.12.1994 JP 323813/94**
**27.12.1994 JP 336883/94**
**27.12.1994 JP 336884/94**

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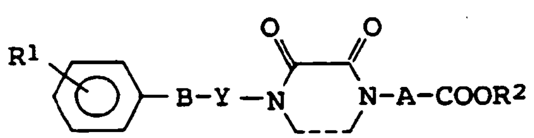
(54) **NOVEL 2,3-DIKETOPIPERAZINE DERIVATIVE OR SALT THEREOF**

(57) The present invention relates to a 2,3-diketopiperazine derivative or a salt thereof, which has inhibitory effect on platelet aggregation because of glycoprotein IIb/IIIa receptor antagonism and hence is useful as a prophylactic and therapeutic agent for diseases associated with platelet aggregation. General formula:




[1]

wherein $R^1$ represents a protected or unprotected amidino group; $R^2$ represents a hydrogen atom or a carboxyl-protecting group; A represents a substituted or unsubstituted lower alkylene group; B represents -O-, -CONH-, -NHCO- or -$SO_2NH$-; Y represents a substituted or unsubstituted lower alkylene group; and the broken line represents a single bond or a double bond.

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isoxazolyl, thiazolyl, isothiazolyl, furazanyl, morpholinyl, furanyl, thienyl, pyranyl, thiopyranyl, benzothienyl, benzoxanyl, indolyl, benzothiazolyl, benzimidazolyl, quinolyl, naphthyridinyl, chromanyl or the like.

The lower alkylene group for A may be substituted by at least one member selected from a lower alkyl group, a lower alkoxy group, a cycloalkyl group, an aryl group, an aralkyl group, a heterocyclic group, a carbamoyl group, a protected or unprotected amino group, a protected or unprotected hydroxyl group, and a protected or unprotected carboxyl group.

The above-exemplified substituents of A may be substituted by at least one member selected from a halogen atom, a lower alkyl group, a lower alkoxy group, a protected or unprotected hydroxyl group, a lower alkylenedioxy group and an aralkyl group.

The lower alkylene group for Y may be substituted by at least one member selected from a lower alkyl group, a lower alkoxy group, a cycloalkyl group, an aryl group, an aralkyl group, a heterocyclic group, and a protected or unprotected hydroxyl group.

The above-exemplified substituents of Y may be substituted by at least one member selected from a halogen atom, a lower alkyl group, a lower alkoxy group, a protected or unprotected hydroxyl group, and an aralkyl group.

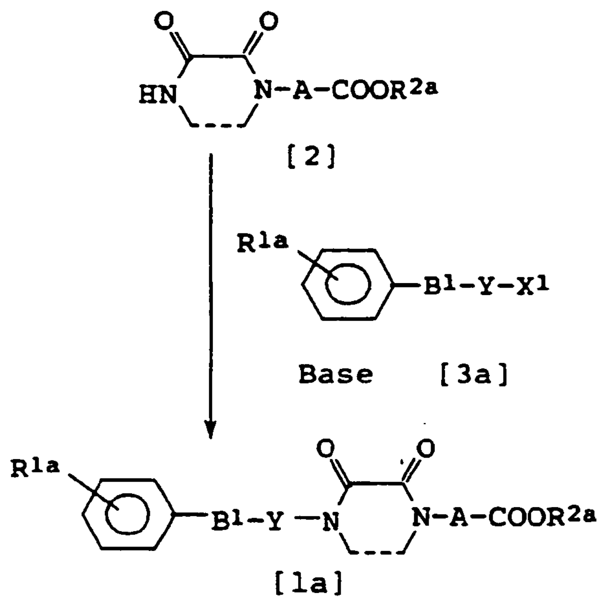
The carboxyl-protecting group includes all the conventional groups usable as carboxyl-protecting groups, for example, lower alkyl groups such as methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, tert-butyl and the like; aryl groups such as phenyl, naphthyl and the like; ar-lower alkyl groups such as benzyl, diphenylmethyl, triphenylmethyl, p-nitrobenzyl, p-methoxybenzyl, bis(p-methoxyphenyl)methyl and the like; acyl-lower alkyl groups such as acetylmethyl, benzoylmethyl, p-nitrobenzoylmethyl, p-bromobenzoylmethyl, p-methanesulfonylbenzoylmethyl and the like; oxygen-containing heterocyclic groups such as 2-tetrahydropyranyl, 2-tetrahydrofuranyl and the like; halogeno-lower alkyl groups such as 2,2,2-trichloroethyl and the like; lower alkylsilylalkyl groups such as 2-(trimethylsilyl)ethyl and the like; acyloxy-lower alkyl groups such as acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl and the like; nitrogen-containing heterocyclic lower alkyl groups such as phthalimidomethyl, succinimidomethyl and the like; cycloalkyl groups such as cyclohexyl and the like; lower alkoxy-lower alkyl groups such as methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl and the like; ar-lower alkoxy-lower alkyl groups such as benzyloxymethyl and the like; lower alkylthio-lower alkyl groups such as methylthiomethyl, 2-methylthioethyl and the like; arylthio-lower alkyl groups such as phenylthiomethyl and the like; lower alkenyl groups such as 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl and the like; and lower alkyl-substituted silyl groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, tert-butylmethoxyphenylsilyl and the like.

The protecting group for each of the amidino group and the amino group includes all the conventional groups usable as amino-protecting groups, for example, acyl groups such as trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, o-bromobenzyloxycarbonyl, (mono-, di- or tri-)chloroacetyl, trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amyloxycarbonyl, tert-butoxycarbonyl, p-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 2-furfuryloxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantyloxycarbonyl, 8-quinolyloxycarbonyl and the like; ar-lower alkyl groups such as benzyl, diphenylmethyl, trityl and the like; arylthio groups such as 2-nitrophenylthio, 2,4-dinitrophenylthio and the like; alkyl- or aryl-sulfonyl groups such as methanesulfonyl, p-toluenesulfonyl and the like; di-lower alkylamino-lower alkylidene groups such as N,N-dimethylaminomethylene and the like; ar-lower alkylidene groups such as benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthylmethylene and the like; nitrogen-containing heterocyclic alkylidene groups such as 3-hydroxy-4-pyridylmethylene and the like; cycloalkylidene groups such as cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxycyclohexylidene and the like; diaryl- or diar-lower alkylphosphoryl groups such as diphenylphosphoryl, dibenzylphosphoryl and the like; oxygen-containing heterocyclic alkyl groups such as 5-methyl-2-oxo-2H-1,3-dioxol-4-yl-methyl and the like; and lower alkyl-substituted silyl groups such as trimethylsilyl and the like.

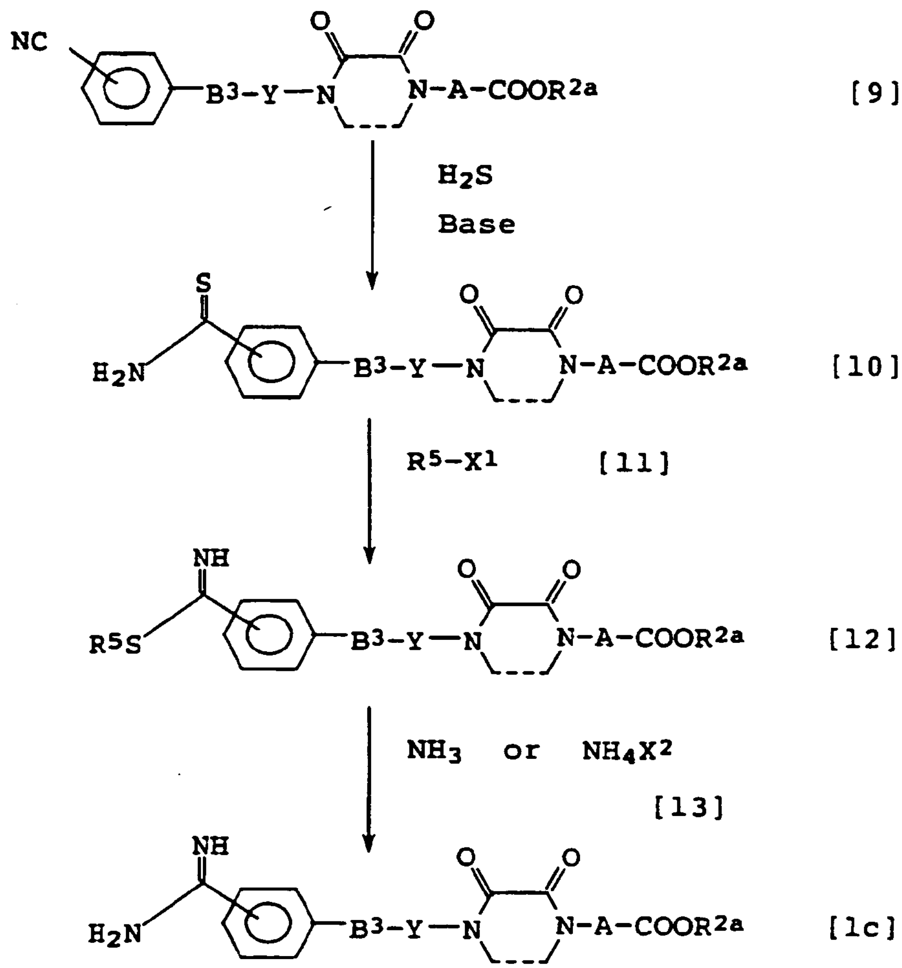
The protecting group for the hydroxyl group includes all the conventional groups usable as hydroxyl-protecting groups, for example, acyl groups such as benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, S-benzylthiocarbonyl, 4-ethoxy-1-naphthyloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl and the like; lower alkyl groups such as methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl and the like; lower alkenyl groups such as allyl and the like; ar-lower alkyl groups such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, trityl and the like; oxygen-containing or sulfur-containing heterocyclic groups such as tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl and the like; lower alkoxy- or lower alkylthio-lower alkyl groups such as methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl and the like; alkyl- or aryl-sulfonyl groups such as methanesulfonyl, p-toluenesulfonyl and the like; and lower alkyl-sub-

- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2-chlorophenyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2,4-dichlorophenyl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(4-chlorophenyl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(3-chlorophenyl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(2-chlorophenyl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(2,4-dichlorophenyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(4-methoxyphenyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(3-methoxyphenyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2-methoxyphenyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2-thienyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(3-thienyl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(2-thienyl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(3-thienyl)propionic acid,
- 3-[4-(3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2-furyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(3-furyl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(2-furyl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(3-furyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(1,3-benzodioxol-5-yl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(1,3-benzodioxol-5-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-2-[(1,3-benzodioxol-5-yl)methyl] propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl)-2-[(1,3-benzodioxol-5-yl)methyl]propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(thiazol-2-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(thiazol-4-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(thiazol-5-yl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(thiazol-2-yl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(thiazol-4-yl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-(thiazol-5-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-[(N-benzyl-N-methyl)carbamoyl]propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-3-[(N-benzyl-N-methyl)carbamoyl]propionic acid,
- 2-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]succinic acid,
- 2-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]succinic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-1,2,3,4-tetrahydro-2,3-dioxopyrazin-1-yl]-3-(pyridin-3-yl)propionic acid,
- 3-[4-[4-(4-Amidinophenoxy)butyl]-1,2,3,4-tetrahydro-2,3-dioxopyrazin-1-yl]-3-(pyridin-3-yl) propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(1-naphthyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2-naphthyl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(benzo[b]thiophen-2-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(benzo[b]thiophen-3-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(benzo[b]thiophen-5-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(benzofuran-2-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(benzofuran-3-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(benzofuran-5-yl)propionic acid,
- 3-[4-[2-(4-Amidinophenoxy)ethyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid,
- 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(butyl)propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid,
- 3-[4-[3-(4-Amidinobenzoylamino)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid,
- [4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]acetic acid,
- [4-[3-(4-Amidinobenzoylamino)propyl]-2,3-dioxopiperazin-1-yl]acetic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-2-yl)propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-4-yl)propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-phenylpropionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-2-phenylpropionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-(1,3-benzodioxol-5-yl)propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-2-(1,3-benzodioxol-5-yl)propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-2-[(1,3-benzodioxol-5-yl)methyl]propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-(thiophen-2-yl)propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-(thiophen-3-yl)propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-methylpropionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl]-3-(cyclopropyl)propionic acid,
- 3-[4-[2-(4-Amidinobenzoylamino)ethyl]-2,3-dioxopiperazin-1-yl)-3-(3-furyl)propionic acid,

[Production process 1]



[Production process 4]



The removing group includes halogen atoms, methanesulfonyl group, p-toluenesulfonyl group, etc.

[Production process 1]

A compound of the general formula [1a] can be produced by reacting a compound of the general formula [2] with a compound of the general formula [3a] in the presence of a base.

Any solvent may be used in this reaction so long as it has no undesirable influence on the reaction. The solvent includes, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl Cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as methylene chloride, chloroform, 1,2-dichloroethane and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used singly or as a mixture thereof. The base used in the reaction includes, for example, inorganic or organic bases such as sodium hydride, metallic sodium, potassium tert-butoxide, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like.

In the reaction, the compound of the general formula [3a] can be used in an amount of 1 to 50 moles, preferably 1 to 3 moles, per mole of the compound of the general formula [2]. The base can be used in an amount of 0.01 to 50 moles, preferably 1 to 3 moles, per mole of the compound of the general formula [2]. Usually, the reaction can be carried out at -20°C to +150°C, preferably +10°C to +100°C for 1 minute to 24 hours.

[Production process 2]

A compound of the general formula [1a] can be produced by reacting a compound of the general formula [4] with a compound of the general formula [5] or a compound of the general formula [6] in the presence of a base.

Any solvent may be used in this reaction so long as it has no undesirable influence on the reaction. The solvent includes, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, propanol and the like; esters such as ethyl acetate and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl Cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as methylene chloride, chloroform, 1,2-dichloroethane and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used singly or as a mixture thereof.

The base includes, for example, inorganic or organic bases such as sodium hydride, metallic sodium, potassium tert-butoxide, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like.

In the reaction, the compound of the general formula [5] can be used in an amount of 1 to 50 moles, preferably 1 to 3 moles, per mole of the compound of the general formula [4]. The compound of the general formula [6] can be used in an amount of 1 to 200 moles, preferably 1 to 50 moles, per mole of the compound of the general formula [4].

The base can be used in an amount of 0.01 to 50 moles, preferably 0.1 to 3 moles, per mole of the compound of the general formula [4].

Usually, the reaction can be carried out at -20°C to +150°C, preferably +10°C to +100°C for 1 minute to 24 hours.

[Production process 3]

A compound of the general formula [1b] can be produced by reacting a compound of the general formula [7] or its reactive derivative substituted at the amino group with a compound of the general formula [8a] reactive derivative substituted at the carboxyl group or with a reactive derivative substituted at the sulfo group of the compound of the general formula [8b].

The reactive derivative of the compound of the general formula [8a] includes acid halides, acid anhydrides, activated amides, activated esters, etc. Preferable examples of the reactive derivative are acid chlorides; acid asides; mixed acid anhydrides with acids (e.g. dialkylphosphoric acids such as dimethylphosphoric acid, diethylphosphoric acid and the like; diphenylphosphoric acid; phosphoric halides such as phosphorus oxychloride, phosphorus pentachloride and the like; dialkylphosphonic acids such as dimethylphosphonic acid, diethylphosphonic acid and the like; sulfonic acids such as sulfurous acid, thiosulfuric acid, sulfuric acid, methanesulfonic acid and the like; and aliphatic carboxylic acids such as acetic acid, propionic acid, pivalic acid, trichloroacetic acid and the like, and aromatic carboxylic acids such as benzoic acid and the like); symmetric acid anhydrides; activated amides with imidazole, dimethylpyrazole, triazole, tetrazole, 1-hydroxy-1H-benzotriazole; activated esters such as cyanomethyl ester, methoxymethyl ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, phenyl thioester, p-nitrophenyl ester, pyranyl ester, pyridyl ester, 8-quinolyl thioester and the like; and esters with N-hydroxy compounds such as N,N-dimethylhydroxylamine, N-hydroxysuccinimide, N-hydroxy-1H-benzotriazole and the like.

The reactive derivative of the compound of the general formula [8b] includes acid chlorides, acid anhydrides, etc.

with ammonia or a compound of the general formula [13].

Any solvent may be used in this reaction so long as it has no undesirable influence on the reaction. The solvent includes, for example, ketones such as acetone and the like; alcohols such as methanol, ethanol and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl Cellosolve and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; and dimethyl sulfoxide. These solvents may be used singly or as a mixture thereof.

The compound of the general formula [13] includes ammonium salts such as ammonium chloride, ammonium bromide, ammonium acetate and the like.

Ammonia or the compound of the general formula [13] can be used in an amount of 1 to 100 moles, preferably 1 to 10 moles, per mole of the compound of the general formula [12] or its salt.

Usually, the reaction can be carried out at 0°C to +150°C, preferably +20°C to +120°C for 1 minute to 24 hours.

[Production process 5]

A compound of the general formula [1d] can be produced by reacting a compound of the general formula [14], its reactive derivative substituted at the carboxyl group, or a salt of the compound of the general formula [14] or the derivative thereof with a compound of the general formula [15], its reactive derivative substituted at the amino group, or a salt of the compound of the general formula [15] or the derivative thereof.

Examples of the reactive derivative of the compound of the general formula [14] substituted at the carboxyl group and the reactive derivative of the compound of the general formula [15] substituted at the amino group are the same reactive derivatives substituted at the carboxyl group or the amino group, respectively, as those exemplified in production process 3.

Examples of the solvent, condensing agent and base which are used in this reaction are the same as those given in production process 3.

The compound of the general formula [15] can be used in an amount of 1 to 20 moles, preferably 1 to 3 moles, per mole of the compound of the general formula [14]. Usually, the reaction can be carried out at -50°C to +150°C, preferably -30°C to +100°C for 1 minute to 24 hours.

[Production process 6]

(1) A compound of the general formula [17] can be produced by reacting a compound of the general formula [9] with a compound of the general formula [16] in the presence of an acid.

In this reaction, the compound of the general formula [16] may be used also as a solvent, or any other solvent may be used so long as it has no undesirable influence on the reaction. This solvent includes, for example, esters such as ethyl acetate and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether and the like; and halogenated hydrocarbons such as methylene chloride, chloroform, 1,2-dichloroethane and the like. These solvents may be used singly or as a mixture thereof.

The acid includes hydrogen chloride, hydrobromic acid, perchloric acid, p-toluenesulfonic acid, methanesulfonic acid, etc.

In the reaction, the compound of the general formula [16] can be used in an amount of 1 to 1,000 moles, preferably 10 to 100 moles, per mole of the compound of the general formula [9].

The acid can be used in an amount of 1 to 200 moles, preferably 5 to 100 moles, per mole of the compound of the general formula [9].

Usually, the reaction can be carried out at -30°C to +150°C, preferably +10°C to +50°C for 30 minutes to 24 hours.

(2) A compound of the general formula [1c] can be produced by reacting the compound of the general formula [17] with ammonia or a compound of the general formula [13].

Examples of the base, the solvent and the compound of the general formula [13] which are used in this reaction are the same bases, solvents and compounds of the general formula [13] as those exemplified in production process 4 (3).

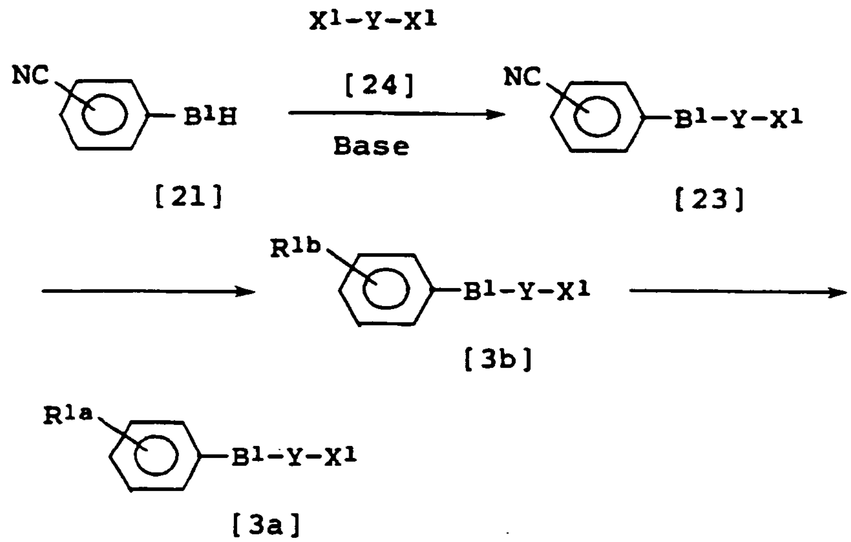
Usually, the reaction can be carried out at 0 to +150°C, preferably +20°C to +120°C for 1 minute to 24 hours.

In the production processes explained above, the compounds of the general formulas [2], [3a], [4], [5], [6], [7], [8a], [8b], [9], [10], [12], [14] and [15] and the reactive derivatives of the compounds of the general formulas [7], [8a], [8b], [14] and [15] may be used in the form of a salt. Examples of the salt are the same salts as those exemplified as the salt of the compound of the general formula [1].

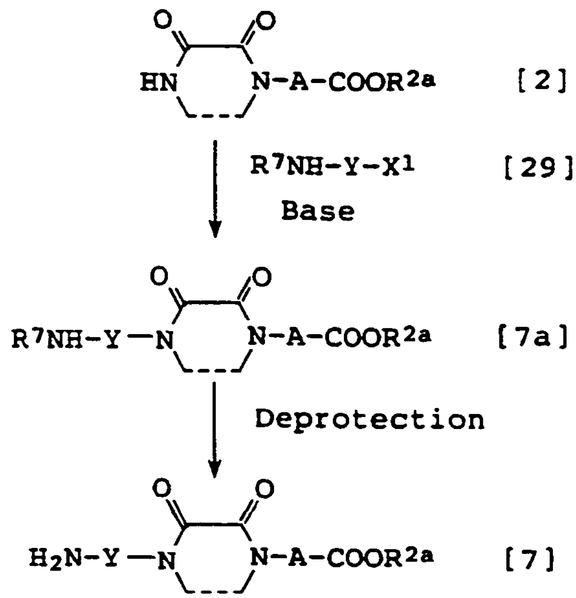
The compounds of the general formula [1a], [1b], [1c] and [1d] can be converted to their respective salts. Examples of the salts are the same salts as those exemplified as the salt of the compound of the general formula [1].

Usually, each of the thus obtained compounds of the general formulas [1a], [1b], [1c] and [1d] or their salts can

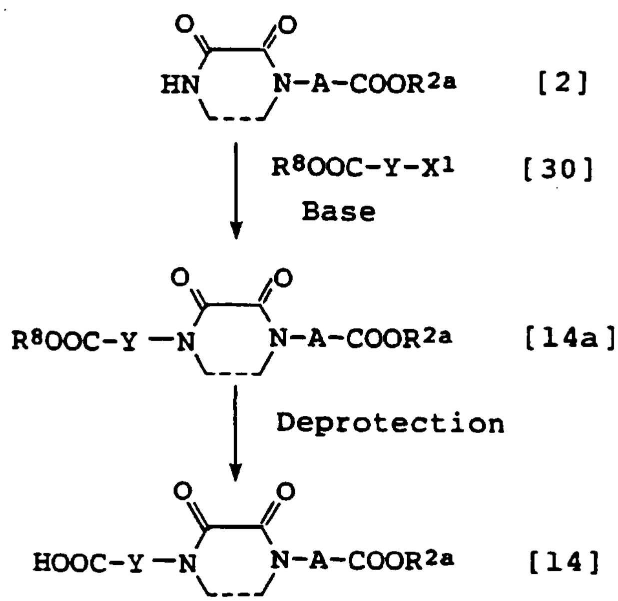
[Production process B]



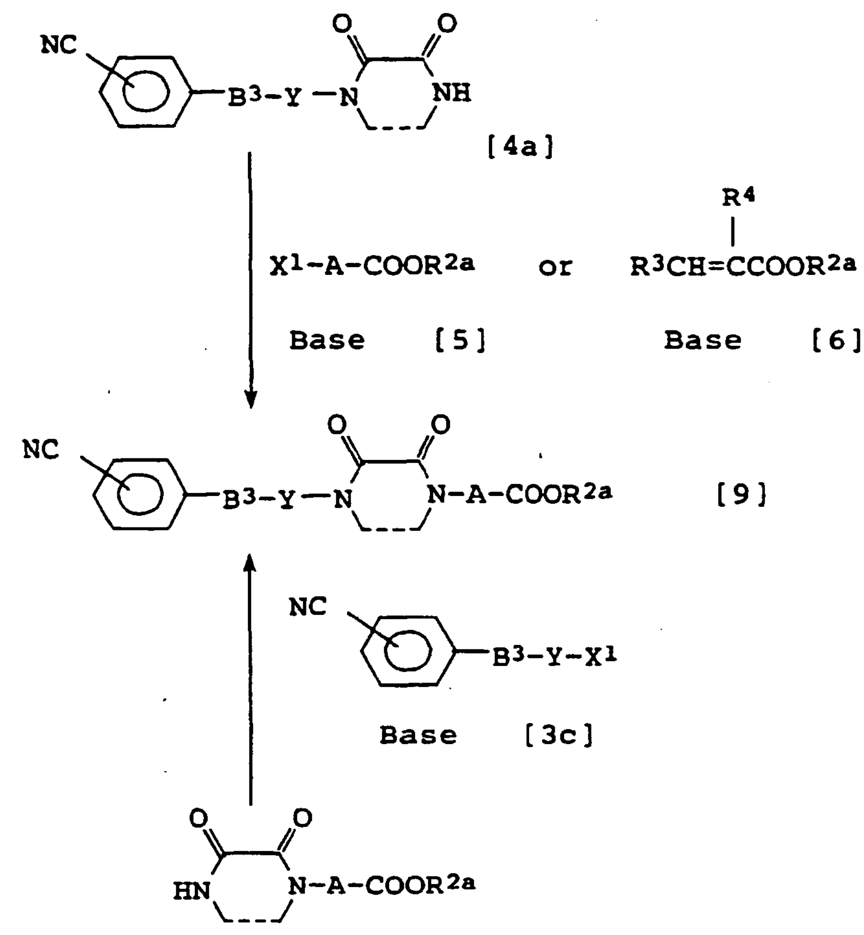
[Production process D]



[Production process E]



[Production process G]




wherein $R^{1b}$ represents an amidino group; $R^7$ represents an amino-protecting group; $R^8$ represents a carboxyl-protecting group; and $R^1$, $R^{1a}$, $R^{2a}$, $R^3$, $R^4$, $R^5$, $R^6$, X, $X^1$, A, $B^1$, $B^2$, $B^3$ and Y are as defined above.

Next, production processes are explained below.

[Production process A]

The compound of the general formula [2] can be obtained by reacting a compound of the general formula [18] with a compound of the general formula [5] or [6] in the presence of a base in the same manner as explained in production process 2, to obtain a compound of the general formula [19], and then subjecting this compound to a well-known reaction for removing the protecting group.

The compound of the general formula [4] can be obtained by reacting a compound of the general formula [18] with the compound of the general formula [3a] in the presence of a base in the same manner as explained in production process 1, to obtain a compound of the general formula [20], and then subjecting this compound to a well-known reaction for removing the protecting group.

[Production process B]

A compound of the general formula [23] is obtained by reacting a compound of the general formula [21] with a compound of the general formula [24] in the presence of a base such as potassium carbonate, potassium tert-butoxide or

pound of the general formula [9] to form a diastereomeric salt, and then recrystallizing the diastereomeric salt from a suitable solvent. It is also possible to convert the thus obtained salt to a free carboxylic acid by removing its base by a per se well-known method.

The compound of the general formula [18] can be synthesized according to, for example, any of the processes described in Yakugaku Zasshi, Vol. 99, No. 9, pp. 929-935 (1979), JP-B-3-57913, etc.

When any of the compounds of the general formulas [1a], [1b], [1c], [1d], [1e], [2], [3a], [3b], [3c], [4], [5], [6], [7], [7a], [8a], [8b], [9], [10], [12], [14], [14a], [15], [17], [19], [20] and [23] to [30] or their salts in the production processes described above has isomers (for example, optical isomers, geometrical isomers, tautomers and the like), these isomers may be used. In addition, the compounds or their salts may be used in the form of a solvate or hydrate or in any of various crystal forms.

When any of the compounds of the general formula [1a], [1b], [1c], [1d], [1e], [2], [3a], [3b], [3c], [4], [5], [6], [7], [7a], [9], [10], [12], [14], [14a], [17] and [19] to [30] or their salts has an amino, carboxyl or hydroxyl group, it is possible to protect the group with a conventional protecting group previously and remove the protecting group by a per se well-known method after completion of the reaction.

The thus obtained compound of the general formula [1] or salt thereof can be isolated and purified according to one or more conventional operations such as extraction, crystallization and/or column chromatography and the like.

When the compound of the present invention is used as a pharmaceutical, it may be properly mixed with a preparation adjuvant such as an excipient, a carrier or a diluent which is usually used for formulation into a pharmaceutical form. The compound can be administered orally or parenterally in the form of tablets, capsules, a powder, a syrup, granules, pills, a suspension, an emulsion, a solution, a powdery formulation, a suppository, an ointment, an injection or the like. The administration route, dose and number of administrations may be properly chosen depending on the age, body weight and symptom of a patient. Usually, the compound may be administered to an adult in a dose of 0.1 to 1,000 mg per day in one portion or several portions orally or parenterally (for example, by injection, drip infusion or intrarectal administration).

Next, the pharmacological activity of typical compounds of the present invention is explained below.

(1) Inhibitory effect on human platelet aggregation

A mixture of blood collected from a human elbow vein and a 3.8% sodium citrate solution in the ratio of 9 : 1 (v/v) was centrifuged at room temperature to obtain platelet-rich plasma and platelet-poor plasma. Then, the platelet-rich plasma was diluted with the platelet-poor plasma to adjust the number of platelets to 5 x $10^8$ platelets/ml. To 150 μl of the diluted platelet-rich plasma was added 18.75 μl of a solution of each test compound in physiological saline, and the resulting mixture was incubated with stirring at 37°C. After 3 minutes, 18.75 μl of adenosine 5'-diphosphate (ADP) (final concentration: 3 μM) was added to the mixture and a change in the intensity of transmitted light caused by the aggregation was recorded with the lapse of time with an aggreometer.

The degree of agglutination in the case of adding only physiological saline was taken as 100% aggregation, and 50% inhibitory concentration ($IC_{50}$) was defined as a concentration of the test compound at which 50% aggregation took place. Table 1 shows the results obtained.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated with reference to the following reference examples and examples, which should not be construed as limiting the scope of the invention.

In the reference examples and the examples, the mixing ratios in the eluents are all by volume, and Silica gel 60, No. 7734 (mfd. by MERCK & CO., INC.) was used as a carrier in the column chromatography and LC-SORB SP-B-ODS (mfd. by Chemco Scientific Co., Ltd.) was used as a carrier in the reversed phase column chromatography. The symbols used in the reference examples and the examples have the following meanings:

| | |
|---|---|
| $d_1$-TFA: | a trifluoroacetic acid-$d_1$, |
| $d_6$-DMSO: | a dimethylsulfoxide-$d_6$, |
| t-Bu: | tert-butyl, |
| DPM: | diphenylmethyl, |
| BOC: | tert-butoxycarbonyl, |
| Cbz: | benzyloxycarbonyl. |

Reference Example 1

1-Bromo-3-(4-cyanophenoxy)propane

In 50 ml of dimethyl sulfoxide was dissolved 10 g of 4-cyanophenol, followed by adding thereto 23 g of potassium carbonate at room temperature. The resulting mixture was stirred at the same temperature for 5 minutes and then 64 ml of 1,3-dibromopropane was added thereto, followed by stirring at room temperature for 12 hours. Subsequently, the reaction mixture was added to a mixed solvent of 200 ml of ethyl acetate and 100 ml of water, after which the organic layer was separated and the aqueous layer was extracted with 50 ml of ethyl acetate. The combined organic layer was washed successively with a 1N aqueous sodium hydroxide solution, water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by a silica gel column chromatography (eluent; hexane : ethyl acetate = 5 : 1) to obtain 5.1 g of 1-bromo-3-(4-cyanophenoxy)propane as a colorless oil.

IR (neat) $cm^{-1}$: $\nu_{CN}$ 2225.
NMR ($CDCl_3$) $\delta$ values: 2.1-2.6 (2H, m), 3.58 (2H, t, J=6Hz), 4.16 (2H, t, J=6Hz), 6.94 (2H, d, J=9Hz), 7.57 (2H, d, J=9Hz).

The following compounds were obtained in the same manner as above.

- 1-Bromo-2-(4-cyanophenoxy)ethane

  IR (KBr) $cm^{-1}$: $\nu_{CN}$ 2225.
  NMR ($CDCl_3$) $\delta$ values: 3.64 (2H, t, J=6Hz), 4.34 (2H, t, J=6Hz), 6.95 (2H, d, J=9Hz), 7.60 (2H, d, J=9Hz).

- 1-Bromo-4-(4-cyanophenoxy)butane

  IR (neat) $cm^{-1}$: $\nu_{CN}$ 2225.
  NMR ($CDCl_3$) $\delta$ values: 1.9-2.2 (4H, m), 3.3-3.6 (2H, m), 4.04 (2H, t, J=5.5Hz), 6.92 (2H, d, J=9Hz), 7.58 (2H, d, J=9Hz).

- 1-Bromo-5-(4-cyanophenoxy)pentane

  IR (KBr) $cm^{-1}$: $\nu_{CN}$ 2225.
  NMR ($CDCl_3$) $\delta$ values: 1.4-2.5 (6H, m), 3.44 (2H, t, J=6Hz), 4.02 (2H, t, J=6Hz), 6.93 (2H, d, J=9Hz), 7.57 (2H, d, J=9Hz).

Reference Example 2

1-Bromo-3-(4-amidinophenoxy)propane hydrochloride

In 200 ml of absolute ethanol was dissolved 20.0 g of 1-bromo-3-(4-cyanophenoxy)propane, and hydrogen chloride gas was introduced thereinto at 0 - 5°C until the solution was saturated therewith. After overnight standing at room tem-

• 1-Bromo-5-(4-benzyloxycarbonylamidinophenoxy)pentane

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($CDCl_3$) δ values: 1.3-2.4 (6H, m), 3.44 (2H, t, J=6Hz), 3.95 (2H, t, J=6Hz), 5.18 (2H, s), 6.83 (2H, d, J=9Hz), 7.1-8.5 (9H, m).

Reference Example 4

4-[3-(4-Benzyloxycarbonylamidinophenoxy)propyl]-1-(2,4-dimethoxybenzyl)-2,3-dioxopiperazine

In 10 ml of N,N-dimethylformamide was dissolved 1.00 g of 1-(2,4-dimethoxybenzyl)-2,3-dioxopiperazine, and 0.17 g of sodium hydride (60%, oil) was added to the solution, followed by stirring at 50°C for 30 minutes. Then, the reaction mixture was cooled to room temperature, after which 1.48 g of 1-bromo-3-(4-benzyloxycarbonylamidinophenoxy)propane was added thereto and the resulting mixture was stirred overnight at the same temperature. The solvent was distilled off under reduced pressure and the resulting residue was purified by a silica gel column chromatography (eluent; chloroform : methanol = 20 : 1) to obtain 1.76 g of 4-[3-(4-benzyloxycarbonylamidinophenoxy)propyl]-1-(2,4-dimethoxybenzyl)-2,3-dioxopiperazine as colorless crystals.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($CDCl_3$) δ values: 1.7-2.5 (2H, m), 3.2-4.2 (14H, m), 4.60 (2H, s), 5.18 (2H, s), 6.3-6.6 (2H, m), 6.7-8.9 (12H, m).

4-[4-(4-Benzyloxycarbonylamidinophenoxy)butyl]-1-(2,4-dimethoxybenzyl)-2,3-dioxopiperazine was obtained in the same manner as above except for using 1-bromo-4-(4-benzyloxycarbonylamidinophenoxy)butane.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1670.
NMR ($CDCl_3$) δ values: 1.5-2.1 (4H, m), 3.2-4.4 (14H, m), 4.59 (2H, s), 5.17 (2H, s), 6.2-6.6 (2H, m), 6.82 (2H, d, J=9Hz), 7.1-8.6 (10H, m).

Reference Example 5

1-[3-(4-tert-Butoxycarbonylamidinophenoxy)propyl]-2,3-dioxopiperazine

In 16.5 ml of anisole was dissolved 8.25 g of 4-[3-(4-benzyloxycarbonylamidinophenoxy)propyl]-1-(2,4-dimethoxybenzyl)-2,3-dioxopiperazine, and 33 ml of trifluoroacetic acid was added to the solution, followed by refluxing for 5 hours. After cooling, the solvent was distilled off under reduced pressure. To the resulting residue was added 40 ml of ethyl acetate, and stirred for 30 minutes, after which the precipitate was collected by filtration and dried to obtain 8.23 g of 4-[3-(4-amidinophenoxy)propyl]-2,3-dioxopiperazine trifluoroacetate. Then, the compound obtained was dissolved in a mixed solvent of 182 ml of dioxane and 82 ml of water, followed by adding thereto 8.37 g of sodium carbonate and 3.62 g of di-tert-butyl dicarbonate, and the resulting mixture was stirred at room temperature for 5 hours. The solvent was distilled off under reduced pressure and 80 ml of ethyl acetate and 80 ml of water were added to the resulting residue and stirred for 30 minutes. The crystals precipitated were collected by filtration and dried to obtain 4.27 g of 1-[3-(4-tert-butoxycarbonylamidinophenoxy)propyl]-2,3-dioxopiperazine as colorless crystals.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1715, 1680, 1625.
NMR ($d_6$-DMSO) δ values: 1.47 (9H, s), 1.7-2.4 (2H, m), 3.2-4.3 (8H, m), 6.91 (2H, d, J=9Hz), 7.8-9.5 (5H, m).

Reference Example 6

1-[4-(4-Benzyloxycarbonylamidinophenoxy)butyl]-2,3-dioxopiperazine

(1) In 3.4 ml of anisole was dissolved 1.7 g of 4-[4-(4-benzyloxycarbonylamidinophenoxy)butyl]-1-(2,4-dimethoxybenzyl)-2,3-dioxopiperazine, and 6.8 ml of trifluoroacetic acid was added to the solution, followed by refluxing for 5 hours. After cooling, the solvent was distilled off under reduced pressure. To the resulting residue was added 10 ml of ethyl acetate, and stirred for 30 minutes, after which the precipitate was collected by filtration and dried to obtain 1.2 g of 4-[4-(4-amidinophenoxy)butyl]-2,3-dioxopiperazine trifluoroacetate.

(2) The compound obtained was dissolved in a mixed solvent of 20 ml of tetrahydrofuran and 10 ml of water, and 0.67 g of sodium carbonate was added thereto, followed by stirring at room temperature for 30 minutes. To the resulting solution was added 0.27 ml of benzyloxycarbonyl chloride and the resulting mixture was stirred at the

IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1730, 1675.
NMR ($CDCl_3$) δ values: 3.1-3.4 (6H, m), 3.7-3.9 (9H, m), 4.54 (2H, s), 5.01 (2H, s), 5.89 (2H, s), 6.4-6.8 (5H, m), 7.1-7.5 (6H, m).

Reference Example 9

Methyl (2,3-dioxopiperazin-1-yl)acetate

A mixture of 10.5 g of methyl [4-(2,4-dimethoxybenzyl)-2,3-dioxopiperazin-1-yl]acetate, 42 ml of trifluoroacetic acid and 21 ml of anisole was refluxed for 4 hours. The reaction mixture was cooled to room temperature and then distilled under reduced pressure to remove the solvent. The resulting residue was purified by a silica gel column chromatography (eluent; chloroform : methanol = 6 : 1) to obtain 4.5 g of methyl (2,3-dioxopiperazin-1-yl)acetate as colorless crystals.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1745, 1680.
NMR ($d_6$-DMSO) δ values: 3.2-3.6 (4H, m), 3.67 (3H, s), 4.21 (2H, s), 8.51 (1H, brs).

The following compounds were obtained in the same manner as above.

- Methyl (1,2,3,4-tetrahydro-2,3-dioxopyrazin-1-yl)acetate

  IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1750, 1685, 1650.
  NMR ($d_6$-DMSO) δ values: 3.74 (3H, s), 4.56 (2H, s), 6.2-6.8 (3H, m).

- Ethyl 4-(2,3-dioxopiperazin-1-yl)butyrate

  IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1735, 1655.
  NMR ($CDCl_3$) δ values: 1.24 (3H, t, J=8Hz), 1.6-2.7 (4H, m), 3.3-3.9 (6H, m), 4.12 (2H, q, J=8Hz), 8.66 (1H, brs).

- Methyl 3-(2,3-dioxopiperazin-1-yl)propionate

  IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1735, 1665.
  NMR ($d_6$-DMSO) δ values: 2.4-2.8 (2H, m), 3.1-3.8 (9H, m), 8.55 (1H, brs).

- Benzyl 2-[(1,3-benzodioxol-5-yl)methyl]-3-(2,3-dioxopiperazin-1-yl)propionate

  IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1730, 1670.
  NMR ($CDCl_3$) δ values: 2.6-4.4 (9H, m), 5.03 (2H, s), 5.87 (2H, s), 6.4-6.8 (3H, m), 7.0-7.6 (5H, m), 8.47 (1H, brs).

Reference Example 10

1-[3-(4-Cyanophenoxy)propyl]-4-(2,4-dimethoxybenzyl)-2,3-dioxopiperazine

This compound was obtained in the same manner as in Reference Example 4.

IR (KBr) $cm^{-1}$: $\nu_{CN}$ 2230, $\nu_{C=O}$ 1680.
NMR ($CDCl_3$) δ values: 1.9-2.4 (2H, m), 3.4-3.7 (6H, m), 3.08 (6H, s), 4.05 (2H, t, J=6Hz), 4.62 (2H, s), 6.3-6.6 (2H, m), 6.93 (2H, d, J=8.5Hz), 7.26 (1H, d, J=9Hz), 7.55 (2H, d, J=8.5Hz).

Reference Example 11

1-[3-(4-Cyanophenoxy)propyl]-2,3-dioxopiperazine

This compound was obtained in the same manner as in Reference Example 6 (1).

IR (KBr) $cm^{-1}$: $\nu_{CN}$ 2220, $\nu_{C=O}$ 1670.
NMR ($d_6$-DMSO) δ values: 1.6-2.3 (2H, m), 3.1-3.8 (6H, m), 3.9-4.5 (2H, m), 7.09 (2H, d, J=9Hz), 7.76 (2H, d,

NMR ($d_6$-DMSO) δ values: 3.1-3.8 (8H, m), 8.63 (1H, brs).

1-(3-Azidopropyl)-2,3-dioxopiperazine was obtained as an oil in the same manner as above.

IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1670.
NMR ($CDCl_3$) δ values: 1.7-2.1 (2H, m), 3.2-3.9 (8H, m), 8.82 (1H, brs).

Reference Example 15

Diphenylmethyl 3-[4-(2-azidoethyl)-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionate

A mixture of 0.5 g of 1-(2-azidoethyl)-2,3-dioxopiperazine, 1.72 g of diphenylmethyl 3-(3-pyridyl)acrylate, 0.2 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene and 2.5 ml of N,N-dimethylformamide was stirred at room temperature for 12 hours. The solvent was distilled off under reduced pressure, after which 30 ml of ethyl acetate and 20 ml of water were added to the resulting residue and the pH was adjusted to 6 with 2N hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with 30 ml of ethyl acetate. The combined organic layer was washed with 20 ml of water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by a silica gel column chromatography (eluent; chloroform : methanol = 20 : 1) to obtain 0.71 g of diphenylmethyl 3-[4-(2-azidoethyl)-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionate as a light-brown oil.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) δ values: 3.1-3.8 (10H, m), 5.8-6.2 (1H, m), 6.84 (1H, m), 7.1-7.9 (12H, m), 8.4-8.8 (2H, m).

The following compounds were obtained in the same manner as above.

- Diphenylmethyl 3-[4-(3-azidopropyl)-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionate

  IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
  NMR ($CDCl_3$) δ values: 1.5-2.0 (2H, m), 2.9-3.9 (10H, m), 5.7-6.1 (1H, m), 6.85 (1H, s), 7.0-8.1 (12H, m), 8.4-8.7 (2H, m).

- Benzyl 3-[4-(2-azidoethyl)-2,3-dioxopiperazin-1-yl]propionate

  IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1730, 1665.
  NMR ($CDCl_3$) δ values: 2.74 (2H, t, J=6Hz), 3.3-3.9 (10H, m), 5.12 (2H, s), 7.34 (5H, s).

- Benzyl 3-[4-(3-azidopropyl)-2,3-dioxopiperazin-1-yl]propionate

  IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1735, 1670.
  NMR ($CDCl_3$) δ values: 1.7-2.1 (2H, m), 2.74 (2H, t, J=6Hz), 3.2-3.9 (10H, m), 5.12 (2H, s), 7.35 (5H, s).

- Benzyl 3-[4-(2-azidoethyl)-2,3-dioxopiperazin-1-yl]-2-[(1,3-benzodioxol-5-yl)methyl]propionate

  IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1730, 1675.
  NMR ($CDCl_3$) δ values: 2.7-3.0 (2H, m), 3.2-3.9 (11H, m), 5.05 (2H, s), 5.90 (2H, s), 6.5-6.8 (3H, m), 7.29 (5H, s).

- Benzyl 3-[4-(3-azidopropyl)-2,3-dioxopiperazin-1-yl]-2-[(1,3-benzodioxol-5-yl)methyl]propionate

  IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1730, 1680.
  NMR ($CDCl_3$) δ values: 1.5-2.3 (2H, m), 2.6-4.1 (13H, m), 5.02 (2H, s), 5.87 (2H, s), 6.5-6.9 (3H, m), 7.1-7.6 (5H, m).

Reference Example 16

Diphenylmethyl 3-[4-(2-aminoethyl)-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionate

A mixture of 0.7 g of diphenylmethyl 3-[4-(2-azidoethyl)-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionate, 0.13 g

Reference Example 18

tert-Butyl [4-(2-azidoethyl)-2,3-dioxopiperazin-1-yl]acetate

In the same manner as in Reference Example 10, 0.7 g of tert-butyl [4-(2-azidoethyl)-2,3-dioxopiperazin-1-yl]acetate was obtained as colorless crystals from 1.0 g of 1-(2-azidoethyl)-2,3-dioxopiperazine and 1.1 g of tert-butyl bromoacetate.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1745, 1670.
NMR ($CDCl_3$) δ values: 1.47 (9H, s), 3.5-3.9 (8H, m), 4.15 (2H, s).

Benzyl [4-(2,4-dimethoxybenzyl)-2,3-dioxopiperazin-1-yl]acetate was obtained as a light-yellow oil in the same manner as in Reference Example 10.

IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1745, 1680.
NMR ($CDCl_3$) δ values: 3.3-3.6 (4H, m), 3.79 (6H, s), 4.26 (2H, s), 4.62 (2H, s), 5.14 (2H, s), 6.3-6.6 (2H, m), 7.1-7.4 (6H, m).

Reference Example 19

tert-Butyl [4-(2-aminoethyl)-2,3-dioxopiperazin-1-yl]acetate hydrochloride

tert-Butyl [4-(2-aminoethyl)-2,3-dioxopiperazin-1-yl]acetate hydrochloride was obtained as an oil from tert-butyl [4-(2-azidoethyl)-2,3-dioxopiperazin-1-yl]acetate in the same manner as in Reference Example 16.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1745, 1670.
NMR ($d_6$-DMSO) δ values: 1.43 (9H, s), 3.6-3.9 (8H, m), 4.10 (2H, s), 8.0-8.7 (3H, brs).

Reference Example 20

Diphenylmethyl (2,3-dioxopiperazin-1-yl)acetate

A mixture of 10.0 g of benzyl [4-(2,4-dimethoxybenzyl)-2,3-dioxopiperazin-1-yl]acetate, 40 ml of trifluoroacetic acid and 20 ml of anisole was refluxed for 2 hours. After completion of the reaction, the solvent was distilled off under reduced pressure and 20 ml of ethyl acetate and 10 ml of diethyl ether were added to the resulting residue, and the solid was collected by filtration. The solid obtained was dissolved in a mixed solvent of 9 ml of ethyl acetate and 1 ml of methanol, followed by adding thereto 25 ml of a 1 M solution of diphenyldiazomethane in ethyl acetate, and the resulting mixture was stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure and the resulting residue was purified by a silica gel column chromatography (eluent; chloroform : methanol = 10 : 1) to obtain 6.8 g of diphenylmethyl (2,3-dioxopiperazin-1-yl)acetate as a white foamy substance.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1745, 1670.
NMR ($d_6$-DMSO) δ values: 3.2-3.8 (4H, m), 4.39 (2H, s), 6.85 (1H, s), 7.2-7.8 (10H, m), 8.67 (1H, brs).

Reference Example 21

Diphenylmethyl [4-[3-(tert-butoxycarbonylamino)propyl]-2,3-dioxopiperazin-1-yl]acetate

In the same manner as in Reference Example 10, 0.68 g of diphenylmethyl [4-[3-(tert-butoxycarbonylamino)propyl]-2,3-dioxopiperazin-1-yl]acetate was obtained as a colorless oil from 1.0 g of diphenylmethyl (2,3-dioxopiperazin-1-yl)acetate and 0.77 g of 1-bromo-3-tert-butoxycarbonylpropane.

IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1745, 1680.
NMR ($CDCl_3$) δ values: 1.42 (9H, s), 1.5-2.1 (2H, m), 3.0-3.7 (8H, m), 4.35 (2H, s), 6.90 (1H, s), 7.3-7.5 (10H, m), 8.00 (1H, brs).

distilled off under reduced pressure and the resulting residue was purified by a silica gel column chromatography (eluent; chloroform : methanol = 20 : 1) to obtain 0.61 g of diphenylmethyl 4-(2,3-dioxopiperazin-1-yl)butyrate as a light-yellow oil.

IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1720, 1685.
NMR ($d_6$-DMSO) δ values: 1.5-2.2 (2H, m), 2.3-2.7 (2H, m), 3.1-4.0 (6H, m), 6.80 (1H, s), 7.1-7.9 (10H, m), 8.51 (1H, brs).

Reference Example 27

Diphenylmethyl 4-(4-tert-butoxycarbonylmethyl-2,3-dioxopiperazin-1-yl)butyrate

With 1.30 g of diphenylmethyl 4-(2,3-dioxopiperazin-1-yl)butyrate was reacted 0.63 ml of tert-butyl bromoacetate by the same method as in Reference Example 12 to obtain 1.48 g of diphenylmethyl 4-(4-tert-butoxycarbonylmethyl-2,3-dioxopiperazin-1-yl)butyrate as a yellow oil.

IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1730, 1680.
NMR ($CDCl_3$) δ values: 1.45 (9H, s), 1.8-2.7 (4H, m), 3.3-3.7 (6H, m), 4.08 (2H, s), 6.85 (1H, s), 7.0-7.4 (10H, m).

Reference Example 28

4-(4-tert-Butoxycarbonylmethyl-2,3-dioxopiperazin-1-yl)butyric acid

By the same process as in Reference Example 16, 0.62 g of 4-(4-tert-butoxycarbonylmethyl-2,3-dioxopiperazin-1-yl)butyric acid was obtained as colorless crystals from 1.30 g of diphenylmethyl 4-(4-tert-butoxycarbonylmethyl-2,3-dioxopiperazin-1-yl)butyrate.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1715, 1665.

Example 1

Methyl [4-[3-(4-benzyloxycarbonylamidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]acetate

A mixture of 1.2 g of methyl (2,3-dioxopiperazin-1-yl)acetate, 0.26 g of sodium hydride (60%, oil) and 12 ml of N,N-dimethylformamide was stirred at room temperature for 30 minutes. Then, 2.52 g of 1-bromo-3-(4-benzyloxycarbonylamidinophenoxy)propane was added thereto and the resulting mixture was stirred at 60°C for 2 hours. The reaction mixture was cooled and then added to a mixed solvent of 40 ml of ethyl acetate and 40 ml of water. After the pH was adjusted to 1 with 2N hydrochloric acid, the aqueous layer was separated. To the aqueous layer was added 40 ml of ethyl acetate and the pH was adjusted to 10 with potassium carbonate. The organic layer was separated and the aqueous layer was extracted with three 20-ml portions of ethyl acetate. The combined organic layer was washed with water and then a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by a silica gel column chromatography (eluent; chloroform : methanol = 30 : 1) to obtain 1.17 g of methyl [4-[3-(4-benzyloxycarbonylamidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]acetate as a colorless oil.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1745, 1675.
NMR ($CDCl_3$) δ values: 1.7-2.3 (2H, m), 3.2-4.3 (13H, m), 5.18 (2H, s), 6.82 (2H, d, J=9Hz), 7.1-7.5 (5H, m), 7.6-9.3 (4H, m).

Examples 2 to 8

The compounds listed in Table 2 were obtained in the same manner as in Example 1.

NMR ($CDCl_3$) δ values: 2.68 (2H, t, J=6Hz), 3.4-4.4 (13H, m), 5.25 (2H, s), 6.87 (2H, d, J=9Hz), 7.2-7.6 (5H, m), 7.6-8.9 (4H, m).

- No. 6

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1740, 1670.
NMR ($CDCl_3$) δ values: 1.9-2.3 (2H, m), 2.65 (2H, t, J=7Hz), 3.5-4.2 (13H, m), 5.19 (2H, s), 6.82 (2H, d, J=9Hz), 7.2-9.3 (9H, m).

- No. 7

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1665.
NMR ($d_6$-DMSO) δ values: 1.16 (3H, t, 7Hz), 1.5-2.1 (2H, m), 2.1-2.6 (2H, m), 3.2-4.4 (12H, m), 5.12 (2H, s), 7.04 (2H, d, J=9Hz), 7.40 (5H, s), 8.03 (2H, d, J=9Hz), 9.11 (2H, brs).

- No. 8

IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1730, 1675.
NMR ($CDCl_3$) δ values: 1.8-2.4 (2H, m), 2.6-4.4 (13H, m), 4.9-5.5 (4H, m), 5.87 (2H, s), 6.4-7.0 (5H, m), 7.1-8.8 (14H, m).

Example 9

The following compound was obtained in the same manner as in Example 1.

- Methyl [4-[3-(4-benzyloxycarbonylamidinophenoxy)propyl]-1,2,3,4-tetrahydro-2,3-dioxopyrazin-1-yl]acetate

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1755, 1690, 1650.
NMR ($d_6$-DMSO) δ values: 1.9-2.6 (2H, m), 3.6-4.3 (7H, m), 4.56 (2H, s), 5.11 (2H, s), 6.60 (2H, s), 6.99 (2H, d, J=9Hz), 7.37 (5H, s), 7.99 (2H, d, J=9Hz), 9.60 (2H, brs).

Example 10

[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]acetic acid hydrochloride

A mixture of 1.05 g of methyl [4-[3-(4-benzyloxycarbonylamidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]acetate, 0.35 g of 5% palladium-carbon, 0.39 ml of 6N hydrochloric acid and 15 ml of methanol was subjected to hydrogenation at ordinary temperature and atmospheric pressure for 3 hours. Then, the pallasium-carbon was filtered off and the solvent was distilled off under reduced pressure to obtain 0.8 g of methyl [4-[3-(4-amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]acetate hydrochloride. The compound obtained was dissolved in 14 ml of 6N hydrochloric acid and the resulting solution was refluxed for 1 hour, after which the solvent was distilled off under reduced pressure to obtain 0.6 g of [4-[3-(4-amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]acetic acid hydrochloride as colorless crystals.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1740, 1670.
NMR ($D_2O$) δ values: 2.0-2.6 (2H, m), 3.2-3.8 (6H, m), 4.05 (2H, s), 4.32 (2H, t, J=6Hz), 7.20 (2H, d, J=9Hz), 7.83 (2H, d, J=9Hz).

Examples 11 to 16

The compounds listed in Table 3 were obtained in the same manner as in Example 10.

NMR ($d_6$-DMSO) δ values: 1.8-4.5 (14H, m), 7.37 (2H, d, J=9Hz), 7.89 (2H, d, J=9Hz), 8.7-10.8 (5H, m).

- No. 16

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1685, 1665.
NMR ($D_2O$) δ values: 1.6-2.8 (4H, m), 3.2-5.0 (10H, m), 7.22 (2H, d, J=9Hz), 7.72 (2H, d, J=9Hz).

Example 17

The following compound was obtained in the same manner as in Example 10.

- [4-[3-(4-Amidinophenoxy)propyl]-1,2,3,4-tetrahydro-2,3-dioxopyrazin-1-yl]acetic acid hydrochloride

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1720, 1685.
NMR ($d_6$-DMSO) δ values: 1.7-2.4 (2H, m), 3.1-4.6 (6H, m), 6.60 (2H, s), 7.08 (2H, d, J=9Hz), 7.87 (2H, d, J=9Hz), 8.6-9.5 (5H, m).

Example 18

Diphenylmethyl α-[4-[4-(4-benzyloxycarbonylamidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-α-phenylacetate

In 5 ml of N,N-dimethylformamide was dissolved 0.2 g of 1-[4-(4-benzyloxycarbonylamidinophenoxy)butyl]-2,3-dioxopiperazine, followed by adding thereto 20 mg of sodium hydride (60%, oil), and the resulting mixture was stirred at 50°C for 30 minutes. The reaction mixture was cooled to room temperature and 0.17 g of diphenylmethyl α-bromophenylacetate was added thereto. After stirring at the same temperature for 2 hours, the reaction mixture was added to a mixed solvent of 20 ml of ethyl acetate and 20 ml of water. The organic layer was separated, washed with water and then a saturated aqueous sodium chloride solution, and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by a silica gel column chromatography (eluent; chloroform : methanol = 20 : 1) to obtain 0.29 g of diphenylmethyl α-[4-[4-(4-benzyloxycarbonylamidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-α-phenylacetate as a colorless oil.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1745, 1675.
NMR ($CDCl_3$) δ values: 1.4-1.9 (4H, m), 2.9-4.1 (8H, m), 5.18 (2H, s), 6.60 (1H, s), 6.7-8.5 (27H, m).

Example 19

α-[4-[4-(4-Amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-α-phenylacetic acid

A mixture of 0.25 g of diphenylmethyl α-[4-[4-(4-benzyloxycarbonylamidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-α-phenylacetate, 0.13 g of 5% palladium-carbon, 0.34 ml of 1N hydrochloric acid and 5 ml of N,N-dimethylformamide was subjected to hydrogenation at ordinary temperature and atmospheric pressure for 3 hours. Then, the pallasium-carbon was filtered off and the filtrate was concentrated under reduced pressure. To the resulting residue were added 2 ml of ethyl acetate, 5 ml of water and 30 mg of sodium hydrogencarbonate to dissolve the residue. The aqueous layer was separated and then purified by a reversed phase column chromatography (eluent: a 50% aqueous acetonitrile solution) to obtain 0.10 g of α-[4-[4-(4-amidinophenoxy)butyl]-2,3-dioxopiperazin-1-yl]-α-phenylacetic acid as colorless crystals.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($d_1$-TFA) δ values: 1.8-2.2 (4H, m), 3.2-4.4 (8H, m), 6.49 (1H, s), 7.14 (2H, d, J=9Hz), 7.3-7.7 (5H, m), 7.79 (2H, d, J=9Hz).

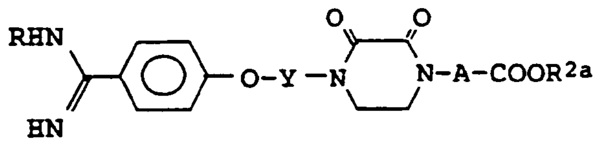
Example 20

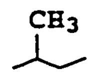
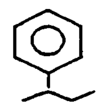
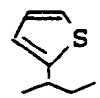
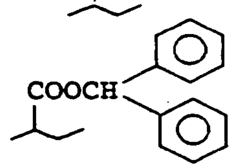
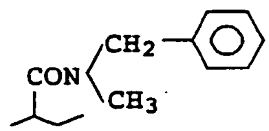
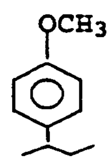
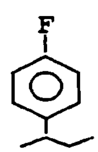
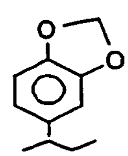
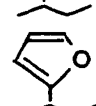
The following compound was obtained in the same manner as in Example 19.

- 2-[(1,3-Benzodioxol-5-yl)methyl]-3-[4-[3-(4-amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]propionic acid

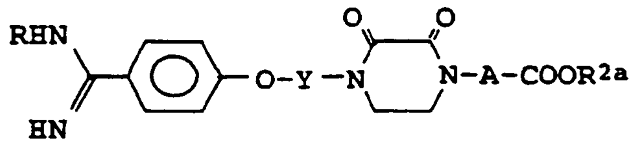
IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1655.
NMR ($d_1$-TFA) δ values: 1.9-2.5 (2H, m), 2.7-4.4 (13H, m), 5.97 (2H, s), 6.5-7.4 (5H, m), 7.79 (2H, d, J=9Hz).

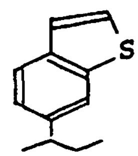
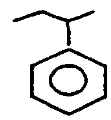
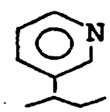
[Table 4]




| Example No. | R | Y | A | $R^{2a}$ |
|---|---|---|---|---|
| 22 | Boc | $-(CH_2)_3-$ |  | DPM |
| 23 | Boc | $-(CH_2)_3-$ |  | DPM |
| 24 | Boc | $-(CH_2)_3-$ |  | DPM |
| 25 | Boc | $-(CH_2)_3-$ |  | DPM |
| 26 | Boc | $-(CH_2)_3-$ |  | DPM |
| 27 | Boc | $-(CH_2)_3-$ |  | DPM |
| 28 | Boc | $-(CH_2)_3-$ |  | DPM |
| 29 | Boc | $-(CH_2)_3-$ |  | DPM |
| 30 | Boc | $-(CH_2)_3-$ |  | DPM |

[Table 6]



| Example No. | R | Y | A | R2a |
|---|---|---|---|---|
| 40 | Boc | $-(CH_2)_3-$ |  | DPM |
| 41 | Boc | $-(CH_2)_3-$ |  | DPM |
| 42 | Boc | $-(CH_2)_3-$ |  | Et |

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) $\delta$ values: 1.26 (3H, d, J=6.5Hz), 1.54 (9H, s), 1.9-2.2 (2H, m), 2.7-3.0 (2H, m), 3.1-3.7 (2H, m), 3.97 (2H, t, J=6Hz), 4.5-5.1 (1H, m), 6.80 (1H, s), 6.85 (2H, d, J=8.5Hz), 7.2-7.5 (10H, m), 7.7-8.2 (4H, m).

- No. 23

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1670.
NMR ($CDCl_3$) $\delta$ values: 1.55 (9H, s), 1.8-2.2 (2H, m), 2.9-3.7 (8H, m), 3.8-4.1 (2H, m), 6.0-6.4 (1H, m), 6.7-7.0 (3H, m), 7.2-8.2 (19H, m).

- No. 24

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1685.
NMR ($CDCl_3$) $\delta$ values: 1.55 (9H, s), 1.9-2.2 (2H, m), 2.8-3.7 (8H, m), 3.98 (2H, t, J=6Hz), 6.1-6.5 (1H, m), 6.7-7.0 (3H, m), 7.2-7.4 (13H, m), 7.6-8.1 (4H, m).

- No. 25

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1685.
NMR ($CDCl_3$) $\delta$ values: 1.55 (9H, s), 1.8-2.2 (2H, m), 3.0-4.4 (10H, m), 4.9-5.3 (1H, m), 6.6-7.0 (4H, m), 7.0-9.0 (24H, m).

- No. 26

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1740, 1675, 1660.
NMR ($CDCl_3$) $\delta$ values: 1.53 (9H, s), 1.7-2.6 (4H, m), 2.7-4.2 (11H, m), 4.2-4.9 (2H, m), 5.7-6.2 (1H, m), 6.84 (1H, s), 6.85 (2H, d, J=8Hz), 7.0-8.8 (19H, m).

- No. 27

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) $\delta$ values: 1.55 (9H, s), 1.8-2.2 (2H, m), 2.8-3.7 (8H, m), 3.79 (3H, s), 3.96 (2H, t, J=6Hz), 6.10 (1H, m), 6.7-6.9 (5H, m), 7.1-8.2 (14H, m).

- No. 28

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1740, 1675.
NMR ($d_6$-DMSO) $\delta$ values: 1.46 (9H, s), 1.7-2.1 (2H, m), 3.2-3.8 (8H, m), 3.8-4.3 (2H, m), 5.8-6.2 (1H, m), 6.7-8.4 (19H, m), 9.0 (2H, bs).

- No. 29

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) $\delta$ values: 1.52 (9H, s), 1.7-2.3 (2H, m), 2.8-4.2 (10H, m), 5.8-6.2 (3H, m), 6.6-7.0 (6H, m), 7.1-8.3 (14H, m).

- No. 30

IR (neat) $cm^{-1}$: $\nu_{C=O}$ 1735, 1685, 1675.
NMR ($CDCl_3$) $\delta$ values: 1.55 (9H, s), 1.8-2.2 (2H, m), 2.8-3.8 (10H, m), 3.8-4.2 (2H, m), 6.0-6.3 (1H, m), 6.7-8.1 (17H, m), 13.5 (2H, bs).

- No. 31

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) $\delta$ values: 1.55 (9H, s), 1.8-2.2 (2H, m), 3.1-4.2 (10H, m), 5.4-5.8 (1H, m), 6.6-9.0 (20H, m).

- No. 32

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1685.
NMR ($CDCl_3$) δ values: 1.23 (3H, t, J=7Hz), 1.55 (9H, s), 1.8-2.3 (2H, m), 3.0-4.5 (12H, m), 5.8-6.2 (1H, m), 6.86 (2H, d, J=9Hz), 7.2-8.3 (6H, m), 8.5-8.7 (2H, m).

- No. 43

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) δ values: 1.54 (9H, s), 1.7-2.3 (2H, m), 2.9-4.2 (10H, m), 5.8-6.3 (1H, m), 6.7-7.6 (17H, m), 7.6-8.7 (4H, m).

- No. 44

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) δ values: 1.54 (9H, s), 1.8-2.3 (2H, m), 2.8-4.2 (10H, m), 5.9-6.3 (1H, m), 6.6-7.4 (16H, m), 7.6-8.5 (4H, m).

- No. 45

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) δ values: 1.55 (9H, s), 1.8-2.3 (2H, m), 2.43 (3H, s), 2.8-4.2 (10H, m), 5.9-6.2 (1H, m), 6.6-8.2 (19H, m), 8.3-8.6 (1H, m).

- No. 46

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) δ values: 1.54 (9H, s), 1.8-2.3 (2H, m), 2.8-4.2 (13H, m), 5.8-6.2 (1H, m), 6.6-7.0 (3H, m), 7.0-8.7 (18H, m).

- No. 47

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.

- No. 48

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) δ values: 1.55 (9H, s), 1.8-2.4 (5H, m), 2.8-4.2 (10H, m), 6.0-6.2 (1H, m), 6.7-7.4 (17H, m), 7.6-8.2 (4H, m).

- No. 49

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) δ values: 1.53 (9H, s), 1.7-2.4 (5H, m), 2.7-4.1 (10H, m), 5.9-6.3 (1H, m), 6.6-7.6 (17H, m), 7.6-8.8 (4H, m).

- No. 50

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1675.
NMR ($CDCl_3$) δ values: 1.55 (9H, s), 1.8-2.4 (2H, m), 2.8-4.1 (13H, m), 5.6-5.9 (1H, m), 6.7-8.7 (20H, m).

- No. 51

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1685.
NMR ($CDCl_3$) δ values: 1.0-2.4 (14H, m), 2.9-4.4 (12H, m), 5.6-6.0 (1H, m), 6.84 (2H, d, J=8.5Hz), 7.85 (2H, d, J=8.5Hz), 8.4-9.3 (5H, m).

ture was heated under reflux for 1 hour. After completion of the reaction, the solvent was distilled off under reduced pressure and 10 ml of ethyl acetate and 10 ml of water were added to the resulting residue, and the pH was adjusted to 7.5 with a saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate, after which the solvent was distilled off under reduced pressure to obtain 0.5 g of ethyl (-)-3-[4-[3-(4-cyanophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionate as colorless crystals having a melting point of 110.5 - 112°C.

IR (KBr) $cm^{-1}$: $\nu_{CN}$ 2220, $\nu_{C=O}$ 1730, 1665.

Example 57

(-)-3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid

In 9 ml of ethanol was suspended 0.45 g of ethyl (-)-3-[4-[3-(4-cyanophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionate, and hydrogen chloride gas was introduced into the suspension under ice-cooling until the suspension was saturated therewith. The resulting solution was allowed to stand overnight at room temperature and then distilled under reduced pressure to remove the solvent. To the resulting residue were added 9 ml of ethanol and 1.2 ml of a 3N solution of ammonia in ethanol, and the resulting mixture was heated under reflux for 3 hours and then distilled under reduced pressure to remove the solvent. To the resulting residue was added 4.5 ml of 6N hydrochloric acid and the resulting mixture was stirred at 70°C for 1 hour. The reaction mixture was cooled to room temperature and adjusted to pH 4.5 with sodium hydrogencarbonate. Purifying the pH-adjusted reaction mixture by a reversed phase column chromatography (eluent: 20% aqueous acetonitrile solution) gave 0.23 g of (-)-3-[4-[3-(4-amidinophenoxy)propyl]-2,3-dioxo-piperazin-1-yl]-3-(pyridin-3-yl)propionic acid as colorless crystals having a melting point of 246 - 248°C (decomp.).

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665: $[\alpha]_d$=-91.7 (C=1.0, $H_2O$)

Example 58

3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid

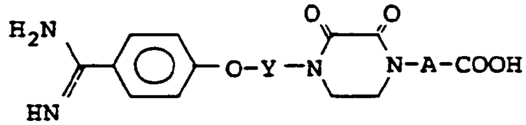
A mixture of 2.3 g of diphenylmethyl 3-[4-[3-(4-tert-butoxycarbonylamidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionate, 18.5 ml of anisole and 37 ml of trifluoroacetic acid was stirred at room temperature for 3 hours and then distilled under reduced pressure to remove the solvent. The resulting residue was suspended in a mixed solvent of 15 ml of ethyl acetate and 13 ml of water, followed by adding thereto 0.55 g of sodium hydrogencarbonate, and the resulting mixture was stirred at room temperature for 30 minutes. The aqueous layer was separated, adjusted to pH 3.5 with a saturated aqueous sodium hydrogencarbonate solution, and then concentrated to a volume of about 10 ml under reduced pressure. The resulting concentrate was purified by a reversed phase column chromatography (eluent: 25% aqueous aeetonitrile solution) to obtain 0.82 g of 3-[4-[3-(4-amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid as colorless crystals.

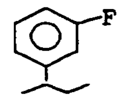
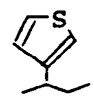
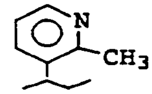
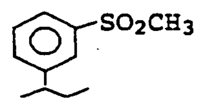
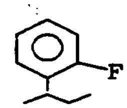
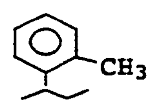
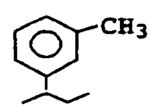
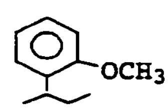
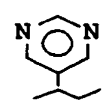
IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1670.
NMR ($d_1$-TFA) $\delta$ values: 2.0-2.5 (2H, m), 3.5-4.5 (10H, m), 5.7-6.1 (1H, m), 7.17 (2H, d, J=9Hz), 7.85 (2H, d, J=9Hz), 8.23 (1H, t, J=7Hz), 8.8-9.1 (2H, m), 9.23 (1H, s).

Examples 59 to 87

The compounds listed in Table 8, Table 9, Table 10 and Table 11 were obtained in the same manner as in Example 58.

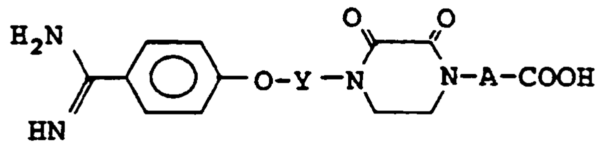
[Table 9]

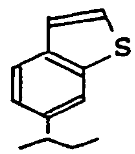
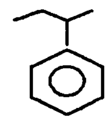



| Example No. | Y | A |
|---|---|---|
| 68 | $-(CH_2)_3-$ |  |
| 69 | $-(CH_2)_3-$ |  |
| 70 | $-(CH_2)_3-$ |  |
| 71 | $-(CH_2)_3-$ |  |
| 72 | $-(CH_2)_3-$ |  |
| 73 | $-(CH_2)_3-$ |  |
| 74 | $-(CH_2)_3-$ |  |
| 75 | $-(CH_2)_3-$ |  |
| 76* | $-(CH_2)_3-$ |  |

*: In place of trifluoroacetic acid, 6N hydrochloric acid was used.

[Table 11]



| Example No. | Y | A |
|---|---|---|
| 86 | $-(CH_2)_3-$ |  |
| 87 | $-(CH_2)_3-$ |  |

Physical properties of the compounds listed in Table 8, Table 9, Table 10 and Table 11 are shown below.

- No. 59

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1680.
NMR ($d_1$-TFA): 1.47 (3H, d, J=7Hz), 2.1-2.5 (2H, m), 2.8-3.1 (2H, m), 3.7-4.1 (6H, m), 4.1-4.4 (2H, m), 4.7-5.3 (1H, m), 7.13 (2H, d, J=9Hz), 7.80 (2H, d, J=9Hz).

- No. 60

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($d_1$-TFA): 2.1-2.4 (2H, m), 3.36 (2H, d, J=8Hz), 3.7-4.4 (8H, m), 6.29 (1H, t, J=8Hz), 7.12 (2H, d, J=8Hz), 7.48 (5H, s), 7.83 (2H, d, J=8Hz).

- No. 61

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1670.
NMR ($d_1$-TFA): 2.0-2.6 (2H, m), 3.38 (2H, d, J=7.5Hz), 3.7-4.0 (6H, m), 4.1-4.4 (2H, m), 6.43 (1H, t, J=7.5Hz), 7.0-7.3 (4H, m), 7.4-7.5 (1H, m), 7.80 (2H, d, J=8Hz).

- No. 62

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($d_1$-TFA): 2.0-2.7 (2H, m), 3.2-4.7 (10H, m), 5.0-5.3 (1H, m), 7.12 (2H, d, J=9Hz), 7.80 (2H, d, J=9Hz).

- No. 63

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1675.
NMR ($d_1$-TFA): 2.0-2.6 (2H, m), 2.9-4.4 (13H, m), 4.7-4.9 (2H, m), 5.9-6.3 (1H, m), 7.0-7.6 (7H, m), 7.80 (2H, d, J=9Hz).

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1670.
NMR ($d_1$-TFA) δ values: 2.0-2.5 (2H, m), 3.2-4.6 (13H, m), 6.0-6.4 (1H, m), 7.0-8.0 (8H, m).

- No. 76

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($D_2O$) δ values: 1.9-2.5 (2H, m), 3.08 (2H, d, J=8Hz), 3.3-4.5 (8H, m), 5.93 (1H, t, J=8Hz), 7.05 (2H, d, J=9Hz), 7.76 (2H, d, J=9Hz), 8.92 (2H, s), 9.19 (1H, s).

- No. 77

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1670.
NMR ($d_1$-TFA) δ values: 2.0-2.5 (2H, m), 3.3-4.5 (10H, m), 6.0-6.4 (1H, m), 6.7-8.0 (7H, m).

- No. 78

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1685.
NMR ($d_1$-TFA) δ values: 2.0-2.5 (2H, m), 3.0-4.6 (13H, m), 5.9-6.5 (1H, m), 6.8-8.2 (8H, m).

- No. 79

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1685, 1670.
NMR ($d_1$-TFA) δ values: 1.8-2.3 (4H, m), 3.5-4.5 (10H, m), 5.8-6.2 (1H, m), 7.14 (2H, d, J=8.5Hz), 7.83 (2H, d, J=8.5Hz), 8.2-8.5 (1H, m), 8.8-9.3 (3H, m).

- No. 80

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1670.
NMR ($d_1$-TFA) δ values: 2.0-2.6 (2H, m), 3.5-4.5 (10H, m), 5.8-6.2 (1H, m), 7.17 (2H, d, J=9Hz), 7.83 (2H, d, J=9Hz), 8.33 (2H, d, J=7Hz), 8.95 (2H, d, J=7Hz).

- No. 81

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1675.
NMR ($d_1$-TFA) δ values: 1.9-2.5 (2H, m), 3.4-4.5 (10H, m), 5.7-6.6 (1H, m), 6.9-9.0 (6H, m).

- No. 82

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($d_1$-TFA) δ values: 0.8-2.0 (9H, m), 2.1-2.5 (2H, m), 2.9 (2H, d, J=8Hz), 3.7-4.6 (8H, m), 4.7-5.2 (1H, m), 7.16 (2H, d, J=9Hz), 7.83 (2H, d, J=9Hz).

- No. 83

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($d_1$-TFA) δ values: 0.3-1.4 (5H, m), 2.1-2.5 (2H, m), 2.9-3.2 (2H, m), 3.7-4.5 (9H, m), 7.14 (2H, d, J=9Hz), 7.81 (2H, d, J=9Hz).

- No. 84

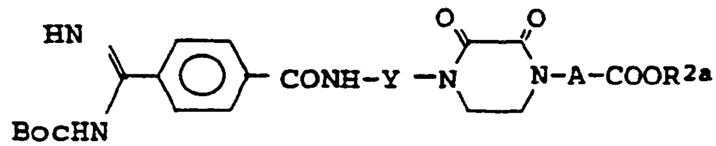
IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($d_1$-TFA) δ values: 2.1-2.5 (2H, m), 3.3-4.5 (10H, m), 6.2-6.6 (1H, m), 6.9-7.4 (3H, m), 7.5-8.3 (8H, m).

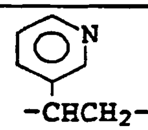
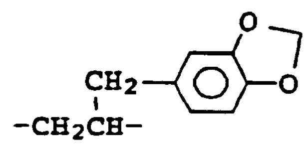
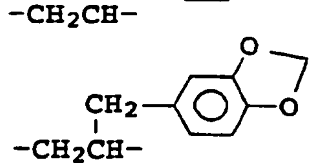
- No. 85

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1665.
NMR ($d_1$-TFA) δ values: 2.0-2.5 (2H, m), 3.1-4.5 (10H, m), 6.8-7.2 (3H, m), 7.3-8.5 (9H, m).

- No. 86

[Table 12]



| Example No. | Y | A | R2a |
|---|---|---|---|
| 90 | $\left( CH_2 \right)_3$ |  | DPM |
| 91 | $\left( CH_2 \right)_2$ | $-CH_2CH_2-$ | DPM |
| 92 | $\left( CH_2 \right)_3$ | $-CH_2CH_2-$ | DPM |
| 93 | $\left( CH_2 \right)_2$ |  | DPM |
| 94 | $\left( CH_2 \right)_3$ |  | DPM |
| 95 | $\left( CH_2 \right)_2$ | $-CH_2-$ | t-Bu |
| 96 | $\left( CH_2 \right)_3$ | $-CH_2-$ | DPM |

Physical properties of the compounds listed in Table 12 are shown below.

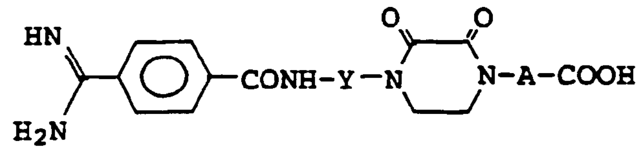
- No. 90

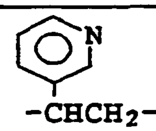
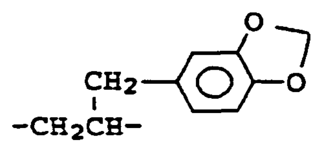
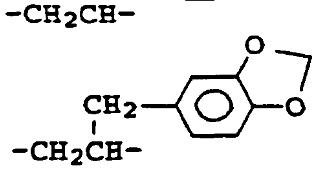
IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1670.
NMR ($d_6$-DMSO) δ values: 1.3-2.1 (11H, m), 3.0-4.2 (10H, m), 5.8-6.2 (1H, m), 6.82 (1H, s), 7.2-9.3 (21H, m).

- No. 91

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1670.
NMR ($CDCl_3$) δ values: 1.54 (9H, s), 2.6-3.0 (2H, m), 3.2-3.8 (10H, m), 6:85 (1H, s), 7.30 (10H, s), 7.6-8.4 (7H,

[Table 13]



| Example No. | Y | A | Salt |
|---|---|---|---|
| 98 | $-(CH_2)_3-$ |  | — |
| 99 | $-(CH_2)_2-$ | $-CH_2CH_2-$ | HCl* |
| 100 | $-(CH_2)_3-$ | $-CH_2CH_2-$ | — |
| 101 | $-(CH_2)_2-$ |  | — |
| 102 | $-(CH_2)_3-$ |  | — |
| 103 | $-(CH_2)_2-$ | $-CH_2-$ | HCl* |
| 104 | $-(CH_2)_3-$ | $-CH_2-$ | HCl* |

* Each hydrochloride was obtained by treating a product obtained by purification by a reversed phase column chromatography, with 6N hydrochloric acid.

Physical properties of the compounds listed in Table 13 are shown below.

- No. 98

sure, after which 5 ml of ethyl acetate and 5 ml of water were added to the residue and the pH was adjusted to 3 with a saturated aqueous sodium hydrogencarbonate solution. The aqueous layer was separated and then concentrated to a volume of about 5 ml. The resulting concentrate was purified by a reversed phase column chromatography (eluent: a 25% aqueous acetonitrile solution) to obtain 0.13 g of [4-[3-(4-amidinobenzenesulfonylamino)propyl]-2,3-dioxopiperazin-1-yl]acetic acid as colorless crystals.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1685, 1655.
NMR ($D_2O$) δ values: 1.6-2.1 (2H, m), 3.02 (2H, t, J=6Hz), 3.3-3.9 (6H, m), 4.02 (2H, s), 8.04 (4H, s).

Example 106

tert-Butyl [4-[4-(4-benzyloxycarbonylamidinophenylamino)-4-oxobutyl]-2,3-dioxopiperazin-1-yl]acetate

To 9 ml of a tetrahydrofuran solution containing 0.18 g of 4-(4-tert-butoxycarbonylmethyl-2,3-dioxopiperazin-1-yl)butyric acid were added 0.16 ml of triethylamine and then 0.15 ml of chlorotrimethylsilane, and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was cooled to -10°C, after which 0.10 ml of oxalyl chloride was added thereto and the resulting mixture was stirred at the same temperature for 30 minutes. Then, 0.15 ml of 4-benzyloxyamidinoaniline and 0.80 ml of triethylamine were added thereto, followed by stirring at the same temperature for 10 minutes and then at 0°C for 1 hour. After completion of the reaction, the insoluble materials were filtered off and the filtrate was concentrated under reduced pressure. The concentrate was purified by a silica gel column chromatography (eluent; chloroform : methanol = 20 : 1) to obtain 0.21 g of tert-butyl [4-[4-(4-benzyloxycarbonylamidinophenylamino)-4-oxobutyl]-2,3-dioxopiperazin-1-yl]acetate as a yellow oil.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1735, 1685.
NMR ($CDCl_3$) δ values: 1.44 (9H, s), 1.8-2.7 (4H, m), 2.8-3.8 (6H, m), 4.05 (2H, s), 5.19 (2H, s), 6.8-7.1 (1H, m), 7.2-7.9 (11H, m).

Example 107

[4-[4-(4-Amidinophenylamino)-4-oxobutyl]-2,3-dioxopiperazin-1-yl]acetic acid

To a solution of 0.28 g of tert-butyl [4-[4-(4-benzyloxycarbonylamidinophenylamino)-4-oxobutyl]-2,3-dioxopiperazin-1-yl]acetate in 2.8 ml of methylene chloride was added 1.4 ml of trifluoroacetic acid, and the resulting mixture was stirred at room temperature for 12 hours and then distilled under reduced pressure to remove the solvent. To the resulting residue were added 0.08 g of 5% palladium-carbon and 5.6 ml of N,N-dimethylformamide, followed by hydrogenation at ordinary temperature and atmospheric pressure for 3 hours. After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. To the resulting concentrate were added 5 ml of water and 0.042 g of sodium hydrogencarbonate to obtain a homogeneous solution. This solution was purified by a reversed phase column chromatography (eluent: a 10% aqueous acetonitrile solution) to obtain 0.08 g of [4-[4-(4-amidinophenylamino)-4-oxobutyl]-2,3-dioxopiperazin-1-yl]acetic acid as colorless crystals.

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1675.
NMR ($d_1$-TFA) δ values: 1.9-3.1 (4H, m), 3.3-4.6 (8H, m), 7.5-8.8 (4H, m).

Example 108

(-)-3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid trihydrate

In 20 ml of water was suspended 3.1 g of the (-)-3-[4-[3-(4-amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid obtained in Example 57, and the suspension was heated to obtain a homogeneous solution. This solution was allowed to stand overnight at room temperature, after which the crystals precipitated were collected by filtration, washed with 3 ml of water, and then dried at room temperature to obtain 2.58 g of (-)-3-[4-[3-(4-amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid trihydrate as colorless crystals having a melting point of 238 - 240°C (decomp.).

IR (KBr) $cm^{-1}$: $\nu_{C=O}$ 1655.
$[\alpha]_d$ -81.5 (C=1.4, $H_2O$)

16. The 2,3-diketopiperazine derivative or its salt according to Claim 15, wherein Y represents a lower alkylene group.

17. The 2,3-diketopiperazine derivative or its salt according to Claim 16, wherein $R^1$ represents an amidino group.

18. The 2,3-diketopiperazine derivative or its salt according to Claim 17, wherein the broken line represents a single bond.

19. The 2,3-diketopiperazine derivative or its salt according to Claim 1, wherein B represents $-SO_2NH-$.

20. The 2,3-diketopiperazine derivative or its salt according to Claim 19, wherein Y represents a lower alkylene group.

21. The 2,3-diketopiperazine derivative or its salt according to Claim 20, wherein $R^1$ represents an amidino group.

22. The 2,3-diketopiperazine derivative or its salt according to Claim 21, wherein the broken line represents a single bond.

23. 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(pyridin-3-yl)propionic acid or its optical isomer, or a salt of either of them.

24. 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-phenylpropionic acid or its optical isomer, or a salt of either of them.

25. 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2-methoxyphenyl)propionic acid or its optical isomer, or a salt of either of them.

26. 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(3-methoxyphenyl)propionic acid or its optical isomer, or a salt of either of them.

27. 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(4-methoxyphenyl)propionic acid or its optical isomer, or a salt of either of them.

28. 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2,3-methylenedioxyphenyl)propionic acid or its optical isomer, or a salt of either of them.

29. 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(thiophen-3-yl)propionic acid or its optical isomer, or a salt of either of them.

30. 3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(2,4-difluorophenyl)propionic acid or its optical isomer, or a salt of either of them.

31. Use of a 2,3-diketopiperazine derivative or a salt thereof as claimed in any one of Claims 1 to 30, as an antithrombotic agent.

32. A pharmaceutical composition comprising a pharmaceutically effective amount of a 2,3-diketopiperazine derivative or a salt thereof as claimed in any one of Claims 1 to 30 and a pharmaceutically acceptable preparation adjuvant.

**INTERNATIONAL SEARCH REPORT**

International application No. PCT/JP95/02391

**A. CLASSIFICATION OF SUBJECT MATTER**

Int. Cl⁶ C07D241/08, A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl⁶ C07D241/08, A61K31/495

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | TAKAKO HORI et. al. "Studies on Antitumor-active 2,3-Dioxopiperazine Derivatives. I. Degradation Products of 1-(2-Chloroethyl)-3-(4-substituted-2,3-dioxo-1-piperazinyl)-alkyl-1-nitrosourea in Aqueous Solution", Chem. Pharm. Bull., (1981), Vol. 29, No. 2, pages 386-389 | 1 - 32 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| January 16, 1996 (16. 01. 96) | February 6, 1996 (06. 02. 96) |
| Name and mailing address of the ISA/ Japanese Patent Office | Authorized officer |
| Facsimile No. | Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1992)